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ORIGINAL ARTICLE

Independent no-reflow predictors in female patients with ST-elevation acute myocardial infarction treated with primary percutaneous coronary intervention

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Abstract Independent no-reflow predictors should be evaluated in female patients with ST-segment elevation acute myocardial infarction (STEMI) and successfully treated with primary percutaneous coronary intervention (PPCI) in the current interventional equipment and techniques, thus to be constructed a no-reflow predicting model. In this study, 320 female patients with STEMI were successfully treated with PPCI within 12 h after the onset of AMI from 2007 to 2010. All clinical, angiographic, and procedural data were collected. Multiple logistic regression analysis was used to identify independent no-reflow predictors. The no-reflow was found in 81 (25.3%) of 320 female patients. Univariate and multivariate stepwise logistic regression analysis identified that low SBP on admission <100 mmHg (OR 1.991, 95% CI 1.018–3.896; $p = 0.004$), target lesion length >20 mm (OR 1.948, 95% CI 1.908–1.990; $p = 0.016$), collateral circulation 0–1 (OR 1.952, 95% CI 1.914–1.992; $p = 0.019$), pre-PCI thrombus score ≥4 (OR 4.184, 95% CI 1.482–11.813; $p = 0.007$), and IABP use before PCI (OR 1.949, 95% CI 1.168–3.253; $p = 0.011$) were independent no-reflow predictors. The no-reflow incidence significantly increased as the numbers of independent predictors increased [0% (0/2), 10.8% (9/84), 14.5% (17/117), 37.7% (29/77), 56.7% (17/30), and 81.8% (9/11) in female patients with 0, 1, 2, 3, 4, and 5 independent predictors, respectively; $p < 0.0001$]. The five no-reflow predicting variables were admission SBP <100 mmHg, target lesion length >20 mm, collateral circulation 0–1, pre-PCI thrombus score ≥4, and IABP use before PCI in female patients with STEMI treated with PPCI.

Keywords ST-elevation acute myocardial infarction · Primary percutaneous coronary intervention · No-reflow · Female

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Introduction

Women differ from men with respect to coronary artery disease epidemiology, symptomatology, pathophysiology, and outcome [1]. PPCI is currently the most effective treatment strategy in acute myocardial infarction (AMI) in women as well as in men [2]. Nevertheless, several studies showed that higher frequency of angiographic no-reflow or slow reflow and higher mortality occurred in women than in men [3, 4]. Furthermore, recent studies showed that female sex was an independent predictor of mortality following AMI [5]. With the current practice to increase use of drug-eluting stents and glycoprotein receptor antagonists as well as shorter delay in the timing of coronary intervention, this study was undertaken to identify independent predictors for no-reflow after PPCI in female patients with STEMI in the contemporary clinical practice.

Materials and methods

Patients

This study is a prospective observational study conducted at two medical institutions. Between January 2007 and January 2010, 320 consecutive female patients who were

admitted within 12 h after the onset of STEMI were enrolled (1,093 male patients during the same enrollment period). All patients signed the informed consent forms. STEMI was defined as the presence of new ST elevation at the J-point in two contiguous leads with the cut-off points: $\geq$0.2 mV in men or $\geq$0.15 mV in women in leads V_2–V_3 and/or $\geq$0.1 mV in other leads, or presumed new left bundle-branch block, and creatine kinase-MB (CK-MB) >1 times normal in patients who had prolonged chest pain lasting $\geq$30 min. Cardiac symptoms lasting >30 min that occurred within 48 h before the onset of infarction were defined as pre-infarction angina.

Maximum creatine kinase-MB were determined from blood samples obtained every 4 h following PPCI. The creatinine clearance (CrCl) was calculated by applying the Cockcroft–Gault formula [6].

Coronary angiography and PPCI

All patients underwent coronary angiography using a common technique. Angiograms were analyzed using a validated quantitative coronary angiographic system (MEDIS, CMS 4.0, Leiden, The Netherlands).

All patients received oral aspirin (300 mg) and clopidogrel (300 mg) immediately after admission and intravenous heparin (5000 U) before PCI. The allocation of coronary angiography and reperfusion therapy was determined by physician's decision. All patients were successfully implanted drug-eluting stents in the infarct-related artery (IRA) after the coronary angiography. Aspiration thrombectomy was performed by more than two passages across the lesion. IABP was inserted in all patients with cardiogenic shock or some patients with Killip class 3 that needed intra-aortic balloon bump (IABP) support before PCI.

Myocardial blush grade (MBG) immediately after PCI were evaluated by two experienced investigators, who were otherwise blinded to all clinical data. The perfusion status of IRA was assessed in accordance with the myocardial blush grade [7]. Angiographic no-reflow can be defined as a TIMI flow grade <3 or 3 with an MBG 0–1 [8]. Collateral vessels were graded according to the report by Rentrop [9]. Thrombus score was modified from Gibson [10].

Statistics

All metric variables were described as mean ± standard deviation. Statistical analysis was performed with the Chi-square test for categorical variables. Student's t test and analysis of variance were used for continuous variables. Univariate and multivariate stepwise logistic regression analysis was performed adjusting diabetes mellitus, age, body mass index (BMI), hypertension, smoking, hyperlipidemia, family history of coronary artery disease (CAD), pre-infarction angina, prior MI, prior PCI, prior coronary artery bypass grafting (CABG), time from pain to PPCI, Killip class, use of cardiovascular medication before AMI, and PCI as reperfusion therapy, physical findings, electrocardiographic findings, admission CrCl, CK-MB, IRA, TIMI flow grade, vessel disease, thrombus score, collateral circulation, reference diameter, lesion diameter, percent stenosis before procedural, target lesion length, stenting methods, post-dilation, stents, stent diameter, post-PCI minimal lumen diameter, maximal inflation pressure, thrombolysis before PCI, intra-aortic balloon bump (IABP) use, tirofiban use, and aspiration thrombectomy.

All statistical processes were performed using SPSS-PC 16.0 (SPSS-PC Inc., Chicago, IL, USA). A p value <0.05 was considered significant.

Results

Patient characteristics

Of the 320 patients who underwent PPCI on an IRA, 81 (25.3%) developed no-reflow after PPCI. Compared to the reflow group, the no-reflow group had significantly lower SBP on admission (101.1 ± 26.7 vs. 114.2 ± 24.4 mmHg, respectively), lower admission DBP (66.0 ± 17.4 vs. 71.5 ± 14.1 mmHg), and significantly higher peak CK values (239 ± 205 vs. 160 ± 166 U/l) ($p < 0.05$ for all). Moreover, the no-reflow group had a significantly larger proportion of Killip classes 2–4 (54.3 vs. 33.1%, respectively) ($p < 0.05$ for all). There were no significant differences between the no-reflow group and the reflow group with respect to age, BMI, hypertension, diabetes mellitus, current smoking, hyperlipidemia, prior MI, prior PCI, prior CABG, pre-infarction angina, family history of CAD, medication before infarction, time from pain to balloon, heart rates, electrocardiographic findings, admission CrCl, and admission plasma glucose and LDL-cholesterol ($p > 0.05$ for all) (Table 1).

Angiographic findings and primary PCI procedure

The angiographic data revealed that the no-reflow group had a significantly larger proportion of low ($\leq$1) initial TIMI flow (84.0 vs. 61.0%, for no-reflow and reflow, respectively), 1 vessel disease (24.7 vs. 13.8%, respectively), collateral flow grades (0–1) (95.1 vs. 82.4%, respectively), pre-PCI thrombus score 2–5 (93.8 vs. 72.8%, respectively), significantly longer target lesion (21.61 ± 9.15 vs. 18.00 ± 7.42 mm, respectively), and significantly more severe stenosis before procedure (99.4 ± 2.2% vs. 97.7 ± 4.6%, respectively) ($p < 0.05$ for all) (Table 2).

Table 1 Baseline clinical characteristics

Variable	No-reflow ($n = 81$)	Normal reflow ($n = 239$)	p value
Age (years)	69.9 ± 8.7	67.7 ± 9.6	0.060
BMI (kg/m^2)	25.6 ± 3.2	25.4 ± 3.1	0.754
Hypertension (%)	53 (65.4)	161 (67.4)	0.750
Diabetes mellitus (%)	22 (27.2)	79 (33.1)	0.324
Current smoking (%)	17 (21.0)	33 (13.8)	0.295
Hyperlipidemia (%)	28 (34.6)	94 (39.3)	0.446
Prior MI (%)	4 (4.9)	15 (6.3)	0.660
Prior PCI (%)	5 (6.2)	21 (8.8)	0.457
Prior CABG (%)	1 (1.2)	0 (0)	0.085
Pre-infarction angina (%)	42 (51.9)	127 (53.1)	0.841
Family history of CAD (%)	4 (4.9)	23 (9.6)	0.190
Medication before MI			
Aspirin (%)	9 (11.1)	45 (18.8)	0.109
ACE inhibitor (%)	7 (8.6)	27 (11.3)	0.382
ARB (%)	2 (2.5)	5 (2.1)	0.846
β blocker (%)	12 (14.8)	53 (22.2)	0.155
Ca channel blocker (%)	37 (45.7)	88 (36.8)	0.158
Statin (%)	4 (4.9)	21 (8.8)	0.448
Oral hypoglycemic drug (%)	5 (13.5)	39 (24.5)	0.148
Insulin (%)	3 (3.7)	10 (4.2)	0.689
Time from pain to PPCI (h)	7.4 ± 7.1	6.4 ± 5.7	0.409
Physical findings on admission			
SBP (mmHg)	101.1 ± 26.7	114.2 ± 24.4	<0.0001
DBP (mmHg)	66.0 ± 17.4	71.5 ± 14.1	0.005
Heart rates (beats/min)	78.6 ± 22.4	75.2 ± 16.7	0.142
Killip classes			<0.0001
1 (%)	37 (45.7)	160 (66.9)	
2 (%)	29 (35.8)	61 (25.5)	
3 (%)	3 (3.7)	12 (5.0)	
4 (%)	12 (14.8)	6 (2.5)	
Electrocardiographic findings			0.524
Anterior wall infarction (%)	45 (55.5)	128 (46.5)	
Inferior wall infarction (%)	36 (44.5)	111 (53.5)	
Admission CrCl (ml/min)	81.0 ± 69.5	90.9 ± 47.9	0.238
Admission plasma glucose (mg/dl)	12.06 ± 5.41	11.09 ± 4.20	0.104
LDL-cholesterol (mmol/l)	2.96 ± 0.73	2.82 ± 0.72	0.141
Peak CK-MB values (U/l)	239 ± 205	160 ± 166	0.003

BMI body mass index, *CAD* coronary artery disease, *CABG* coronary artery bypass grafting, *ACE* angiotensin-converting enzyme, *ARB* angiotensin receptor blocker, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *LDL* low-density lipoprotein

Among the procedural features, the no-reflow incidence was significantly higher in patients who had more post-dilation (54.3 vs. 30.9%, for no-reflow and reflow, respectively), ≥2 stents (37.0 vs. 31.0%), and much IABP use before PCI (24.9 vs. 5.8%, respectively) ($p \leq 0.05$ for all) (Table 2).

However, IRA, reference diameter, target lesion diameter, stenting methods, stent diameter, post-PCI minimal lumen diameter, maximal inflation pressure, tirofiban use and aspiration thrombectomy showed no difference between the two groups ($p > 0.05$ for all) (Table 2).

Independent no-reflow predictors

Univariate and multivariate stepwise logistic regression analysis identified that SBP on admission <100 mmHg (OR 1.991, 95% CI 1.018–3.896; $p = 0.004$), target lesion length >20 mm (OR 1.948, 95% CI 1.908–1.990; $p = 0.016$), collateral circulation 0–1 (OR 1.952, 95% CI 1.914–1.992; $p = 0.019$), pre-PCI thrombus score ≥4 (OR 4.184, 95% CI 1.482–11.813; $p = 0.007$), and IABP use before PCI (OR 1.949, 95% CI 1.168–3.253; $p = 0.011$) were independent no-reflow predictors (Table 3).

Table 2 Angiographic and PCI characteristics

Variable	No-reflow ($n = 81$)	Normal reflow ($n = 239$)	p value
IRA			0.303
LAD (%)	44 (54.3)	106 (42.5)	
LCX (%)	6 (7.4)	28 (11.7)	
RCA (%)	31 (38.3)	102 (42.7)	
LMA (%)	0 (0)	3 (1.3)	
Initial TIMI flow			0.001
0–1 (%)	68 (84.0)	146 (61.0)	
2 (%)	6 (7.4)	19 (7.9)	
3 (%)	7 (8.6)	74 (31.1)	
Vessel disease			0.027
1 (%)	20 (24.7)	33 (13.8)	
2 (%)	13 (16.0)	64 (26.8)	
3 (%)	48 (59.3)	142 (59.4)	
Pre-PCI thrombus score			0.001
0–1 (%)	5 (6.2)	65 (27.1)	
2 (%)	1 (1.2)	14 (5.9)	
3 (%)	2 (2.5)	6 (2.5)	
4 (%)	8 (9.9)	15 (6.3)	
5 (%)	65 (80.2)	139 (58.2)	
Collateral circulation			0.030
0–1 (%)	77 (95.1)	197 (82.4)	
2 (%)	3 (3.7)	34 (14.2)	
3 (%)	1 (1.2)	8 (3.4)	
Reference diameter (mm)	3.25 ± 0.47	3.25 ± 0.81	0.967
Target lesion diameter (mm)	3.14 ± 0.45	3.09 ± 0.45	0.337
Percent stenosis before procedural (%)	99.4 ± 2.2	97.7 ± 4.6	0.002
Target lesion length (mm)	21.61 ± 9.15	18.00 ± 7.42	<0.0001
Stenting			0.733
Stenting after pre-dilation (%)	78 (96.3)	228 (95.4)	
Direct stenting (%)	3 (3.7)	11 (4.6)	
Post-dilation (%)	44 (54.3)	74 (30.9)	<0.0001
Stents per patient			0.028
1 (%)	51 (63.0)	165 (69.0)	
≥2 (%)	30 (37.0)	74 (31.0)	
Stent diameter (mm)	3.01 ± 0.30	3.02 ± 0.53	0.825
Post-PCI minimal lumen diameter (mm)	2.86 ± 0.47	2.91 ± 0.45	0.446
Maximal inflation pressure (atm)	15.2 ± 3.0	16.0 ± 3.2	0.061
IABP use before PCI (%)	22 (27.2)	25 (10.5)	<0.0001
Tirofiban use (only tirofiban in China) (%)	68 (84.0)	215 (90.0)	0.144
Aspiration thrombectomy (%)	60 (74.1)	170 (71.1)	0.611

The no-reflow incidence and independent predictors

The no-reflow incidence significantly increased as the numbers of independent predictors increased [0% (0/2), 10.8% (9/84), 14.5% (17/117), 37.7% (29/77), 56.7% (17/30), and 81.8% (9/11) in patients with 0, 1, 2, 3, 4, and 5 independent predictors, respectively; $p < 0.0001$)] (Fig. 1).

Discussion

Rapid restoration of coronary flow to the jeopardized myocardium has become an essential part of therapy after AMI. Despite an open IRA, breakdown of obstruction to coronary microvasculature can markedly decrease blood flow to the infarct zone. This phenomenon is important

Table 3 Univariate and multivariate logistic regression for the no-reflow predictors

Variables	Univariate analysis		Multivariate analysis	
	p value	OR (95% CI)	*p* value	OR (95% CI)
SBP on admission <100 mmHg	<0.0001	1.022 (1.011–1.033)	0.004	1.019 (1.006–1.032)
Target lesion length >20 mm	0.002	1.951 (1.921–1.982)	0.016	1.948 (1.908–1.990)
Collateral circulation 0–1	0.009	1.726 (1.148–2.594)	0.019	1.952 (1.914–1.992)
Pre-PCI thrombus score ≥4	<0.0001	3.669 (3.548–3.815)	0.007	4.184 (1.482–11.813)
IABP use before PCI	0.003	1.894 (1.898–2.996)	0.011	1.949 (1.168–3.253)

The Nagelkerke R^2, a measure of predictive capability, for the model is 0.787

OR odds ration, *CI* confidence interval

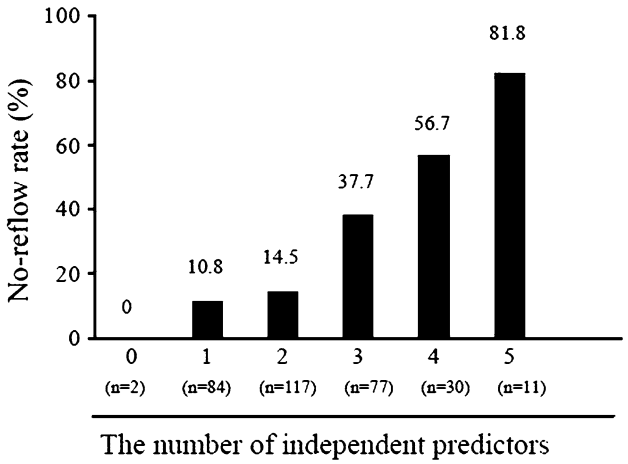

Fig. 1 No-reflow rate according to the number of independent predictors

because it correlates with infarct size, short- and long-time mortality, and provides useful prognostic information [11].

In the present study, the no-reflow rate after PPCI was 25.3%, which was consistent with previously published no-reflow rates of 5–25% [12]. SBP on admission <100 mmHg, target lesion length >20 mm, collateral circulation 0–1, pre-PCI thrombus score ≥4, and IABP use before PCI were independent no-reflow predictors.

A systolic arterial BP (ABP) <120 mmHg in patients with AMI was associated with a higher mortality than in patients with ABP >120 mmHg [13]. A low SBP (<120 mmHg) decreased coronary blood flow (CBF), collateral blood flow, and increased infarct size [14, 15]. Based on these data, low normal BP is associated with decreased CBF. Furthermore, this decreased CBF accelerates leukocyte accumulation, enhances the trapping of leukocytes in capillaries, and adhesion of leukocytes in venules, and enhances the no-reflow.

Most acute coronary syndromes result from plaque rupture or fissuring with superimposed thrombus formation. Microvascular embolization of plaque material and thrombus content can occur spontaneously or iatrogenically during the PCI procedure [16]. An intravascular ultrasound study showed that high atherothrombotic burden and decreased plaque volume may be risk factors for development of the no-reflow during stent implantation in patients with AMI [17]. Furthermore, a recent study found that fibrofatty volume over the entire lesion length was the only independent factor for no-reflow and slow reflow during PPCI [18]. These studies indicate that not only thrombus burden but also plaque material determines the development of no-reflow. The longer the target lesion, the larger the plaque burden. Our study demonstrates that female patients with a target lesion length >20 mm were about twofold more likely to develop the no-reflow than those with a target lesion length ≤20 mm.

Well-developed collateral circulation theoretically augments microvascular reperfusion by preserving anatomical patency of the vasculature, and enhancing myocardial viability and microvascular integrity within the occluded IRA territory. Collateral flow may prolong the maximal time of coronary occlusion before reperfusion when irreversible transmural myocardial necrosis develops, and reduce infarct size [19]. Well-developed collaterals (≥2) before reperfusion by PCI in patients with STEMI are associated with a protective effect on coronary microcirculation and decreasing no-reflow [20, 21].

Distal embolism of thrombus plays a major role in no-reflow. However, TIMI thrombus grades cannot provide information regarding the no-reflow prediction on subsequent PCI. A previous study showed that specific angiographic morphologic features of high-burden thrombus formation were independent no-reflow predictors in 794 patients with AMI after PPCI [22], but these predictors are very complex to guide subsequent PCI and adjunctive therapies. Our study is in accordance with a previous study [23], showing that pre-PCI thrombus score ≥4 was one of no-reflow predictors.

Our study demonstrates that all patients with cardiogenic shock, and some patients with Killip class 3 on admission that needed IABP support, and not all patients with Killip class 3 on admission, had a higher no-reflow incidence. A linear association between Killip class and

postprocedural TIMI 3 flow was also observed in the Shock Trial Registry [24]. Killip class ≥3 at presentation may be a consequence of a larger infarction that may be associated with more severe damage of microvascular bed and decreasing coronary perfusion pressure, thus explain that the patients with IABP use had higher no-reflow incidence in our study. The cardiac cells within the no-reflow area were swollen by microscopic examination. The capillary endothelium was damaged and exhibited areas of regional swelling with large intraluminal protrusions that in some cases appeared to plug the capillary lumen [25]. Cellular edema and cell contracture compressing the capillaries may contribute to the microvascular compression [26]. A higher rate of distal embolization was found in patients with advanced Killip class, which may partially explain the no-reflow observed in these patients [27].

Limitations

The no-reflow prediction model should be confirmed in large-scale prospective studies in the future. The major limitation is the absence of a core-lab, although angiographic data were analyzed with similar criteria. The no-reflow was diagnosed without the assistance of myocardial contrast echocardiography. Hence, the evaluation of coronary microcirculation was insufficient.

Conclusions

The five no-reflow predicting variables were SBP on admission <100 mmHg, target lesion length >20 mm, collateral circulation 0–1, pre-PCI thrombus score ≥4, and IABP use before PCI in patients with STEMI treated with PPCI. Therefore, the prediction model provides a basis for therapeutic decision-making. Because most patients with STEMI have a combination of these factors, combined treatment strategies are preferred to improve patient outcomes, such as aspiration thrombectomy, adenosine, or glycoprotein IIb/IIIa inhibitors [28].

Conflict of interest The authors have no conflicts of interest to report.

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